PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

BRASS, Daniel
Dizengoff Street 10
64281 Tel Aviv
ISRAËL

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
07 August 2000 (07.08.00)	
Applicant's or agent's file reference	**International application No.**
D01/5	PCT/IL00/00364

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

DEXCEL LTD. (for all designated States except US)
LAHAV, Raffael et al (for US)

International filing date	:	21 June 2000 (21.06.00)
Priority date(s) claimed	:	22 June 1999 (22.06.99)
Date of receipt of the record copy by the International Bureau	:	11 July 2000 (11.07.00)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EE, ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA, MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US, UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Marie-José Devillard

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 March 2001 (19.03.01)	
International application No. PCT/IL00/00364	**Applicant's or agent's file reference** D01/5
International filing date (day/month/year) 21 June 2000 (21.06.00)	**Priority date** (day/month/year) 22 June 1999 (22.06.99)
Applicant LAHAV, Raffael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 December 2000 (18.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRASS, Daniel
Plinner, Bodner, Brass
Beit Agish Ravad
13 Noach Mozes Street
Tel Aviv 67442
ISRAËL

Date of mailing (day/month/year)
19 March 2001 (19.03.01)

Applicant's or agent's file reference
D01/5

IMPORTANT NOTIFICATION

International application No.
PCT/IL00/00364

International filing date (day/month/year)
21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
BRASS, Daniel
Dizengoff Street 10
64281 Tel Aviv
Israel

State of Nationality

State of Residence

Telephone No.
972-3-620-1866

Facsimile No.
972-3-620-1469

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
BRASS, Daniel
Plinner, Bodner, Brass
Beit Agish Ravad
13 Noach Mozes Street
Tel Aviv 67442
Israel

State of Nationality

State of Residence

Telephone No.
972-3-696-9090

Facsimile No.
972-3-696-6656

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and
Administrative Instructions, Section 417)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as International Preliminary Examining Authority

Date of mailing (day/month/year)	
19 March 2001 (19.03.01)	
International application No.	International filing date (day/month/year)
PCT/IL00/00364	21 June 2000 (21.06.00)
Applicant	
DEXCEL LTD. et al	

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRASS, Daniel
Plinner, Bodner, Brass
Beit Agish Ravad
13 Noach Mozes Street
Tel Aviv 67442
ISRAËL

Date of mailing (day/month/year)
19 March 2001 (19.03.01)

Applicant's or agent's file reference
D01/5

IMPORTANT NOTIFICATION

International application No.
PCT/IL00/00364

International filing date (day/month/year)
21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
BRASS, Daniel
Dizengoff Street 10
64281 Tel Aviv
Israel

State of Nationality:
State of Residence:
Telephone No.: 972-3-620-1866
Facsimile No.: 972-3-620-1469
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
BRASS, Daniel
Plinner, Bodner, Brass
Beit Agish Ravad
13 Noach Mozes Street
Tel Aviv 67442
Israel

State of Nationality:
State of Residence:
Telephone No.: 972-3-696-9090
Facsimile No.: 972-3-696-6656
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

REC'D 30 OCT 2001

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference D01/5	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL00/00364	International filing date *(day/month/year)* 21 JUNE 2000	Priority date *(day/month/year)* 22 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant DEXCEL LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 DECEMBER 2000	17 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BLESSING FUBARA Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IL00/00364

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-21 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 22-26 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IL00/00364

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	NONE	YES
	Claims	1-39	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-39	NO
Industrial Applicability (IA)	Claims	1-39	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-39 lack novelty under PCT Article 33(2) as being anticipated by Bergstrand et al. (US Patent No. 5,817, 338) referred herein after as the '338 patent.

The '338 patent discloses a pharmaceutical multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers, or an alkaline salt of omeprazole or one of its single enantiomers. The composition further comprises mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium lauryl sulfate, hydroxypropyl methyl cellulose, methacrylic acid copolymer, triethyl citrate, mono- and di-glycerides, polysorbate 80 and sodium stearyl fumarate. The dosage composition comprises a core of active omeprazole, a separating layer, an enteric coating pellets and material and tableting composition. The omeprazole tablet formulation is also formulated without a separating layer. See abstract, columns 3-8, examples 1-17 and claims 1-25. The '338 patent thus anticipates the claimed invention.

Claims 1-39 meet the criteria set out in PCT Article 33(4), because the instant invention directed to coated benzimidazole derivative such as omeprazole composition formulated into an enteric coated tablet form finds utility in the pharmaceutical formulation industry.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 9/00, 9/14, 9/16, 9/20, 9/22, 9/28, 9/50 and US Cl.: 424/400, 464, 465, 468, 474, 489, 490, 494, 495

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL00/00364

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/00, 9/14, 9/16, 9/20, 9/22, 9/28, 9/50
US CL :424/400, 464, 465, 468, 474, 489, 490, 494, 495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/400, 464, 465, 468, 474, 489, 490, 494, 495

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,013,281 A (LUNDBERG et al.) 11 January 2000, see abstract, column 5, line 6 to column 6 and line 49, column 7, line 27 to column 8, and line 24, examples 1-7 and claims 1-6 and 15-21.	1-39
X	US 5,817,338 A (BERGSTRAND et al.) 06 October 1998, see entire document.	1-39
X	US 5,753,265 A (BERGSTRAND et al.) 19 May 1998, see columns 5 and 6, column 7 line 43 to column 10, and line 48, examples 1-16 and claims 1-11, 14, 15, 17 and 19.	1-39
X	US 4,853,230 A (LOVGREN et al.) 01 August 1989, see entire document.	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 SEPTEMBER 2000	24 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer BLESSING FUBARA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-8374

Form PCT/ISA/210 (second sheet) (July 1998)*

APPLICATION FOR PATENT

TITLE: STABLE BENZIMIDAZOLE FORMULATION

INVENTORS: RAFFAEL LAHAV and VALERIE AZOULAY

This Application is a Continuation-in-Part Application of PCT Application No. PCT/IL00/00364, filed on June 21, 2000, and also claims priority from Israeli Patent Application No. 130602, filed on June 22, 1999, both of which are hereby incorporated by reference as if fully set forth herein.

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a novel stable formulation for an acid labile benzimidazole, and methods of preparation and administration thereof, and in particular, for a stable formulation of a benzimidazole which is suitable for oral administration.

Omeprazole, Pantoprazole, Lansoprazole and other derivatives of benzimidazole, which are active proton pump inhibitors and used conventionally for decreasing gastric secretion are known to be susceptible to degradation and transformation in acid media. Omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is disclosed and described in European Patent No. 5129 and European Patent No. 124495, as well as in numerous other patents and published patent applications.

The susceptibility of these active proton pump inhibitor substances to degradation and transformation in acid media increases the difficulty of preparing a pharmaceutical form designed for oral administration. If the active substance comes into contact with the

stomach content, which is a highly acidic medium, these chemical substances become degraded. Thus, these benzimidazole derivatives should be protected both during storage and during their passage through the acidic environment of the stomach.

The stability of Omeprazole has been extensively studied (see for example A. Pilbrant and C. Cederberg, *Scan. J. Gastroenterol.*, **20**: 113-120, 1985). Omeprazole degrades with a half-life of less than 10 minutes in an environment with pH values below 4.0. At pH 6.5, the half life of Omeprazole is 18 hours and at pH 11 about 300 days. Therefore, the environment of Omeprazole should be kept at a sufficiently high pH value in order to maintain the stability of the compound, in a formulation which is suitable as a product for oral administration, for example by locating Omeprazole within a core which also contains alkaline constituents. This leads to an alkaline reaction aimed at improving stability of the active substance during manufacture thereof and during storage of the pharmaceutical formulation.

In addition, such a formulation must protect Omeprazole from the acidic environment of the stomach, since if Omeprazole is given orally without any protective coating, it will degrade in the acid environment of the stomach. European Patent No. 237,200 discloses one solution, which is to directly coat the solid core containing Omeprazole, or another benzimidazole derivative, with an enteric coating layer.

However, this apparent solution to the instability of Omeprazole caused further complications, in that the alkaline core containing Omeprazole was found to react with the enteric coating, thereby causing the enteric coating to degrade. A solution to these further complications is disclosed in United Kingdom Patent Application No. 2,189,698, in which Omeprazole is contained within a solid active core, which is coated first with a

subcoating layer and then with an enteric coating layer. The enteric coating layer protects the Omeprazole during the passage through the stomach, while the subcoating layer protects the enteric coating layer from reacting negatively with the alkaline core containing Omeprazole.

The background art describes other attempts to provide formulations which are suitable for oral administration of acid-labile substances. For example, PCT Application No. WO 97/12581 discloses a composition adapted for oral administration containing Omeprazole which specifically does not include alkaline-reacting compounds. Instead, the composition features a core composed of a nuclei and Omeprazole compressed together, an intermediate layer and an enteric layer.

European Patent Application No. 519,144 discloses a formulation for Omeprazole, which features a neutral (sugar) core. Omeprazole is sprayed onto the sugar core, after which an intermediate coating layer and an enteric coating layer are sprayed onto the core.

PCT Application No. WO 98/00114 discloses a modification to other background art formulations for Omeprazole, in which the intermediate subcoating layer is partially neutralized with an alkaline compound. However, this modified formulation still features the subcoating layer, which is a disadvantage in that it complicates the manufacturing process and increases the expense and difficulty of manufacture. Thus, the formulation disclosed in PCT Application No. WO 98/00114, like those disclosed in European Patent Application No. 519,144 and other background art references, has the disadvantage of requiring the intermediate layer.

PCT Application No. WO 83/00435 discloses a solid dosage form, such as a capsule or tablet, containing a pharmacologically active agent coated with an anionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7. The preferred anionic polymer is a partly methyl esterified methacrylic acid polymer in which the ratio of free carboxylic groups to ester groups is about 1:2. In contrast to the present invention, Omeprazole is not disclosed as one of the active agents.

French Application No. 2,692,146 discloses stable compositions of microgranules of gastro-protected Omeprazole. The composition features a center of Omeprazole diluted in mannitol. This center is coated with an intermediate layer featuring mannitol. An enteric coating is then added over this intermediate layer. PCT Application No. WO 97/12581 discloses a formulation in which an intermediate layer between the core and an enteric coating contains silicium dioxide.

PCT Application No. WO 96/37195 discloses a formulation which lacks a subcoating layer, but which features a core containing titanium dioxide. Both the core containing Omeprazole and the enteric coating layer placed on top of the core include titanium dioxide as an ingredient. Unfortunately, titanium dioxide is only able to mask the discoloration caused by the reaction between Omeprazole and the enteric coating layer, but cannot prevent such an undesirable reaction. Thus, the disclosed formulation does not prevent the undesirable reaction between the benzimidazole derivative and the enteric coating, which is known in the art.

German Patent Application No. 196 26 045 A1 discloses a method for stabilising Omeprazole by coating small tablets or pellets, containing large amounts of mannitol,

with a subcoating of Eudragit L. The subcoating of Eudragit L is neutralized , after which a final enteric coat of non-neutralized Eudragit L is applied.

A formulation of a benzimidazole derivative, such as Omeprazole, which lacks an intermediate coating layer and yet which is stable both during storage and during the passage through the stomach, would be highly desirable. Such a formulation would be simpler to manufacture and would expose the sensitive benzimidazole derivative to fewer production steps, thereby decreasing the possibility that the active compound would degrade during production. Unfortunately, such a stable benzimidazole formulation, which lacks an intermediate layer, is not currently available.

There is thus a unmet need for, and it would be useful to have, a stable benzimidazole formulation, particularly for Omeprazole which lacks an intermediate layer and yet which is stable both during storage and during the passage through the stomach.

SUMMARY OF THE INVENTION

The formulation of the present invention contains a benzimidazole derivative, such as Omeprazole, and is able to maintain the stability of this active ingredient without a separating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the optional addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this pH range, the enteric coating is optionally

applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material.

The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach, where the acidic environment of the stomach causes a partial ionic exchange to occur within the material of the coating. This partial ionic exchange renders the coating impermeable to the acidic liquids of the stomach. On the other hand, during storage the problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the "enteric coat" is no longer acidic during the storage period..

Preferably, the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof, as well as any other derivatives of benzimidazole which are proton pump inhibitors and which are conventionally used to decrease gastric secretion.

According to the present invention, there is provided a stable composition for a benzimidazole derivative, the composition comprising: (a) a substrate, the substrate featuring the benzimidazole derivative; and (b) an enteric coating material layered over the substrate, the enteric coating material having a pH value of at least about 6.5.

The substrate can optionally have several different structures. For example, the substrate is optionally an active core containing the benzimidazole derivative, in which the core is a pellet, bead or tablet for example. The active core can be prepared by any conventional method known in the art, including but not limited to, pellets prepared by

spheronisation, pellets prepared by coating an inert non pareil seed with Omeprazole, tablets prepared by granulation and compression, as well as any other methods.

The enteric coating material optionally and preferably includes an enteric material selected from the group consisting of hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

More preferably, the enteric coating material further comprises an alkaline compound, such that the pH value is adjusted by adding the alkaline compound to the enteric material. Most preferably, the alkaline compound is an inorganic or organic alkaline salt compound. Even more preferably, the alkaline compound is selected from the group consisting of basic sodium, potassium or ammonium hydroxide. Also most preferably, the pH value is in a range of from about 7 to about 10.

The enteric coating material of the composition could optionally include a plasticizer. Preferably, the plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

According to another embodiment of the present invention, there is provided a stable composition for a benzimidazole derivative, the composition consisting essentially of: (a) a substrate, the substrate featuring the benzimidazole derivative; and (b) an enteric coating material layered over the substrate, the enteric coating material having a pH value of at least about 6.5.

According to still another embodiment of the present invention, there is provided a method for producing a stable composition for a benzimidazole derivative, the method

comprising the steps of: (a) forming a substrate with the benzimidazole derivative; (b) preparing an enteric coating material having a pH value of at least about 6.5; and (c) layering the enteric coating material over the substrate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The formulation of the present invention contains a benzimidazole derivative, such as Omeprazole, and is able to maintain the stability of this active ingredient without a separating layer between the active compound and an enteric coating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this pH range, the enteric coating is optionally applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material.

The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach. The problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the enteric coat at this stage is no longer acidic.

Without wishing to be limited to a single mechanism, it is hypothesized that as the formulation passes through an acidic environment, such as the acidic environment of the stomach, the outer layer of the enteric coat is converted to an acidic form. This acidic form of the enteric coating material is insoluble in the acidic environment of the stomach.

If the formulation is then placed in an environment with a more alkaline pH value, for example by moving into the small intestine, the enteric coat dissolves and releases the active substance.

The use of an enteric coating which includes HPMCP (hydroxypropylmethylcellulose phthalate) neutralized with a basic salt is disclosed in U.S. Patent No. 5,225,202 and in two scientific articles, "Enteric Film Coating Using Completely Aqueous Dissolved Hydroxypropyl Methyl Cellulose Phthalate Spray Solutions" (J.W. Stafford *et al., Drug Development and Industrial Pharmacy*, **8**:513-530, 1982) and "The In Vitro and In Vivo Performance of Aqueous Based Enteric Coats of Neutralized Hydroxypropyl Methyl Cellulose Phthalate" (J.R. Bloor *et al.*, *Drug Development and Industrial Pharmacy*, **15**:2227-2243, 1989). However, the disclosed enteric coating is not taught or suggested in any of these references as a suitable direct enteric coating for substrates which contain Omeprazole. As noted previously, Omeprazole and the related benzimidazole derivatives are unusually sensitive molecules, and as such must be carefully protected. Furthermore, U.S. Patent No. 5,225,202 teaches the necessity for a subcoat between the drug-containing substrate and the enteric coating for drugs which are not compatible with the enteric coating. By contrast, the present invention has been shown to be highly effective without such a subcoat, which is particularly surprising since the background art teaches that formulations containing Omeprazole or another benzimidazole derivative must also feature a subcoat. Neither scientific article even considers the problems associated with acid-sensitive drugs, and as such cannot teach or suggest the formulation of the present invention.

As shown by both the *in vitro* and *in vivo* data given below, the formulation of the present invention has been shown to be particularly effective for the oral administration of Omeprazole as the exemplary benzimidazole derivative, a result which could not have been predicted from these references. Indeed, the article by J.R. Bloor *et al.* teaches away from the use of such a neutralized enteric coating for any formulation, as this article disclosed good *in vitro* performance of the formulation but poor *in vivo* performance. By contrast, as described in greater detail below with regard to Example 7, the formulation of the present invention shows good performance *in vivo*. Thus, the background art neither teaches nor suggests the direct coating of a substrate containing Omeprazole or another benzimidazole derivative with an enteric coating material having a pH value of at least about 6.5, and in fact teaches away from such a formulation.

The preparation of the benzimidazole-containing compositions of the present invention is described first with reference to the following general description and then with reference to the following non-limiting examples of the preparation and application of the compositions of the present invention.

As noted previously, the formulation of the present invention includes a substrate which features the benzimidazole derivative. A solution is prepared with the enteric coating material, which has a pH value of at least 6.5 and more preferably of from about 7 to about 10. Preferably, a pH value in the desired range is obtained by adding an alkaline compound to an enteric coating material. More preferably, the alkaline compound is selected from the group consisting of sodium, potassium or ammonium hydroxide. This enteric coating solution is then layered directly over the substrate to form the composition of the present invention.

The term "substrate" refers to substantially any structure which features the benzimidazole derivative, such as Omeprazole. For example, this structure could be an active core containing the benzimidazole derivative. This active core could be prepared in a number of different ways which are known in the art. For example, the active core could be formed by compressing the benzimidazole derivative with an alkaline substance. As another example, the active core could be prepared by mixing the benzimidazole derivative with an alkaline substance, spheronizing the mixture and then forming cores through pelletisation. As yet another example, the active core is optionally and preferably prepared by embedding the active ingredient in a poloxamer and compressing the embedded material into tablets. The active core is also optionally formed by granulating the active ingredient with an alkaline substance and compressing the granulation into tablets.

Alternatively and optionally, the structure could include a neutral core, such as a sugar bead which does not contain the benzimidazole derivative, over which the benzimidazole derivative is coated. The coating includes Omeprazole or other benzimidazole derivative with a suitable adhesive polymer.

The substrate optionally and preferably includes a basic stabilizing material, which is more preferably at least one of sodium stereate and arginine, particularly for the active coating. Magnesium carbonate and/or sodium hydrogen carbonate may also optionally be used as basic stabilizing materials, in addition to, or alternatively in place of, these materials.

Substantially any type of neutralized suitable enteric coating material could be used in order to coat the benzimidazole substrate, including but not limited to, cellulose

acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); polyvinyl acetate phthalate; cellulose acetate trimellitate; polymethacrylic acid methyl methacrylate or ethyl methacrylate, such as the various types of Eudragit; and hydroxypropyl methylcellulose acetate succinate (HPMCAS). However, preferably the enteric coating material is prepared with the proviso that this material does not contain HPMCP alone, but only in combination with at least one of these other listed enteric coating materials. More preferably, HPMCP is not present in the enteric coating material. The particularly preferred enteric coating material is HPMCAS.

As used herein, the term "neutralized enteric coating material" refers to enteric coating material which has been at least partially neutralized by reaction with an alkaline compound, which is optionally a basic inorganic salt. Preferably, the enteric coating material is at least about 60 % neutralized, more preferably the enteric coating material is at least about 80 % neutralized, and most preferably the enteric coating material is at least about 95 % neutralized.

The enteric coating optionally contains a plasticizer, such as a citric acid ester, a phthalic acid ester, or any suitable plasticizer.

The method for applying the enteric coating material to the substrate can vary. Substantially any coating method can be used, such as pan coating or fluidized bed coating, with the solution of the enteric coat chosen. As noted previously, preferably this solution is an aqueous solution. The enteric coating materials described previously can be applied to the substrate in an aqueous solution if the pH value of the solution is adjusted to at least 6.5, and more preferably to an alkaline value, most preferably a pH value from about 7 to about 10.

The following specific examples illustrate various aspects of the compositions of the present invention, and are not intended to be limiting in any way. Specific reference is made to Omeprazole for the purposes of description only and without intending to be limiting.

Example 1

This example of the composition of the present invention was prepared as follows. The substrate was in the form of an active core, which was prepared by embedding Omeprazole in poloxamer (Pluronic PE 6800), granulating the resulting mass, adding the necessary auxiliary substances to the mass, and compressing the resultant material into tablets. The substrate was then coated with alkaline polyvinyl acetate phthalate as the enteric coating layer.

Substrate (Active Embedded Core)

Ingredients	Quantity per tablet
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Magnesium carbonate	10 mg
Sodium starch glycolate	12 mg
Titanium dioxide	100 mg
Ludipress ®	226 mg
Sodium stearyl fumarate	25 mg

Enteric coating layer

Polyvinyl acetate phthalate	75 mg
Antifoam emulsion	0.25 mg
Sodium hydroxide	12 mg

For the preparation of the substrate, the poloxamer was melted at a temperature of 80 °C. Omeprazole, together with 2 mg colloidal silicon dioxide, 8 mg of magnesium carbonate, titanium dioxide and 6 mg of sodium starch glycolate were added and mixed thoroughly. Mixing was continued until the melt solidified. The melt was granulated and the rest of the ingredients added to the granulate. The granulate was then compressed into tablets which contained 20 mg Omeprazole. These tablets, which formed the substrate of the composition, were then transferred into a conventional coating pan and coated with

the enteric coating layer, prepared in the following manner. First, the antifoam emulsion was dissolved in water to form an aqueous solution. Polyvinyl acetate phthalate was then stirred into this solution for a final concentration of about 10% weight per volume before sodium hydroxide was added. Sodium hydroxide (1 M solution) was then added to adjust the pH value of the solution to about 8, thereby obtaining a basic solution of the enteric coating material. This solution was then sprayed onto the tablets with an incoming air temperature of 40 °C.

Example 2

This example of the composition of the present invention was prepared as follows. The substrate was prepared by embedding Omeprazole in poloxamer (Pluronic PE 6800) to form tablets, as for Example 1. However, in this Example, the tablets were then coated with hydroxypropyl methylcellulose acetate succinate (HPMCAS) as the enteric coating layer.

Substrate

Ingredients	**Quantity per tablet**
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Sodium starch glycolate	20 mg
Ludipress ®	228 mg
Sodium stearyl fumarate	25 mg

Enteric coating layer

Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)	43 mg
Triethyl citrate	12 mg
Sodium lauryl sulfate	1.3 mg
Talc	21.4 mg
Sodium hydroxide	2.3 mg

The tablets were prepared as for Example 1, except that titanium dioxide was omitted. The tablets were then coated in a conventional coating pan with the enteric coating solution, which was prepared as follows. First, triethyl citrate was dissolved in water to form an aqueous solution. Sodium lauryl sulfate was then added to this aqueous solution. The HPMCAS and talc were dispersed in this solution, such that the concentration of HPMCAS was about 10% weight per volume. Sodium hydroxide (1M solution) was then added to adjust the pH value of the solution to a value from about 7 to about 10. The enteric coating was layered over the substrate by spraying the solution with an incoming air temperature of 40 °C.

Example 3

This example of the composition of the present invention was prepared as for Example 1, except that the enteric coating contained alkaline HPMCP (hydroxypropylmethylcellulose phthalate) rather than HPMCAS.

Substrate

Ingredients	Quantity per tablet
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Sodium starch glycolate	10 mg
Titanium dioxide	83 mg
Ludipress ®	145 mg
Sodium stearyl fumarate	25 mg

Enteric coating layer

HPMC Phthalate (HP-55)	56.2 mg
Triethyl citrate	22.5 mg
Sodium hydroxide	9 mg

The substrate was prepared as described in Example 1, and was then coated in a conventional coating pan with the enteric coating solution by spraying the solution at an incoming air temperature of 40 °C. The enteric coating solution was prepared as follows. The HPMC phthalate was suspended in the water to a concentration of about 10% weight per volume (before sodium hydroxide was added). Sodium hydroxide (1M solution) was then added to this aqueous suspension until the HPMCP dissolved. The resultant solution has a pH value in a range of from about 8 to about 10. The triethyl citrate was then added

to the resultant solution in order to form the enteric coating solution, which was then layered over the substrate as previously described.

Example 4

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution. Hard gelatin capsules were then filled with the resultant pellets.

Substrate

Neutral core	**Quantity per capsule**
Sugar spheres 20/25 (700-850 microns)	161.63 mg

Active coating

Ingredients	**Quantity per capsule**
Omeprazole	20.00 mg
Hydroxypropyl methylcellulose 2910	5.33 mg
Hydroxypropyl cellulose	6.00 mg
Lactose	8.00 mg
Disodium phosphate anhydrous	0.64 mg
Sodium lauryl sulfate	0.50 mg

Enteric coating layer

HPMCAS	21.00 mg
Triethyl citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
Talc	11.00 mg
Sodium hydroxide	1.12 mg

The composition of the present invention was prepared according to this Example as follows. First, sugar spheres were placed in a fluid bed coating chamber, equipped with a Wurster bottom spraying device. A suspension of the ingredients in water was then prepared so that the concentration was approximately 20 % of total solids in water. This active coating suspension was sprayed onto the sugar spheres. A suspension of the enteric coating was prepared according to Example 2. This enteric coating was then sprayed onto the substrate in order to form the finished pellets. The pellets were then placed in capsules.

Example 5

This example of the composition of the present invention was prepared with a compressed tablet as the substrate. The tablet was then coated with alkaline HPMCAS (Hydroxypropyl Methylcellulose Acetate Succinate) as the enteric coating layer, preferably having a pH in a range of from about 7 to about 10.

Substrate (Active Compressed Tablet Core)

Ingredients	Quantity per tablet
Omeprazole	20 mg
Lactose	192.5 mg
Magnesium carbonate	10 mg
Sodium starch glycolate	10 mg
Povidone	10 mg
Sodium stearyl fumarate	7.5 mg

Enteric coating layer

HPMCAS	16.1 mg
Triethyl citrate	4.5 mg
Sodium lauryl sulfate	0.5 mg
Talc	8.04
Sodium hydroxide	0.86 mg

For the preparation of the substrate, Omeprazole, together with lactose, magnesium carbonate, sodium starch glycolate, and povidone were mixed thoroughly. The mixture was then granulated with a sufficient quantity of water, and dried. Sodium stearyl fumarate was then added to the mixture, which was then compressed into tablets weighing 250 mg each.

These tablets, which formed the substrate of the composition, were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 6

Stability tests were performed with formulations prepared according to Examples 2 and 3. For the first test, both coated and uncoated tablets prepared according to either Example 2 or Example 3 were placed into a box which was open to the environment. The open box was then stored at 40 °C and 75 % relative humidity, which are very stringent conditions. The coated and uncoated tablets were examined initially, after a week and after a month to determine stability. The results are shown in the tables below.

Tablets Prepared According to Example 2

Sampled Material	Appearance of Sample		
	Initial	After One Week	After One Month
coated tablet	off white	deeper off white	deeper off white
uncoated tablet	white	white	white

Tablets Prepared According to Example 3

Sampled Material	Appearance of Sample		
	Initial	After One Week	After One Month
coated tablet	off white	off white	deeper off white
uncoated tablet	white	white	white

The term "deeper off white" refers to a more intense off white color which was observed for some samples, as described in greater detail above. These results show that coated tablets prepared according to either Example 2 or Example 3 showed good stability, even after one month of storage under particularly stringent conditions.

In a second stability test, coated tablets were prepared according to Example 2. These coated tablets were then packed into an Alu/Alu (Aluminum/Aluminum) blister, which is a well known technique in the art for packing certain oral dosage forms. The blister was then stored under accelerated conditions of 30 °C and 60% relative humidity; or 40 °C and 75% relative humidity. Samples of the tablets were examined initially, and after one month of storage under one of these conditions. In addition, samples were assayed to determine the amount of Omeprazole present in the coated tablet, as listed under "Assay" as milligrams of Omeprazole per tablet. A dissolution test was performed, using the accepted USP method. The coated tablets were placed in 0.1 N HCl for 2 hours, followed by a solution at pH 6.8 with stirring with a paddle at 100 rpm for 15 minutes, 30 minutes or 45 minutes. Gastric resistance was also examined by placing the coated tablets in a simulated gastric fluid for 2 hours (pH of approximately 1), as is well known in the art. The results are shown in the table below.

	Time (min)	Initial	30^0 60 % RH	40^0 75% RH
Description	NA	Off white	Off white	Off white
Assay	NA	20.4 mg	19.39 mg	19.66 mg
Dissolution	120	0%	0%	0%
	135	52%	42%	39%
	150	96%	85%	90%
	165	105%	99%	104%
Gastric Resistance	NA	101%	98%	96%

These results show that the coated tablets, prepared according to Example 2, show good stability and gastric resistance, yet are also able to dissolve in an appropriate time-dependent manner.

Example 7

A one-way pharmacokinetic pilot study was performed *in vivo* for testing the pharmacokinetic profile of the coated tablets, which were prepared according to Example 2. The study was performed with ten healthy male volunteers, who received a single dosage of the coated tablets, containing 20 mg of Omeprazole. The results showed that Omeprazole administered in the coated tablets of the present invention had a similar lag time to absorption in comparison to a previous study performed with the reference product, which is the 20 mg Omeprazole dosage form of the formulation of Astra (Aktiebolaget Hassle),

and also as described in the literature (see for example Duvauchelle, T. *et al.*, "Comparative Bioavailability Study of Two Oral Omeprazole Formulations After Single and Repeated Administrations in Healthy Volunteers", *Pharmacokinetics*, **16**: 141-149, 1998). The lag time to absorption is defined as the time between the administration of the formulation and the first detection of the active ingredient in the samples taken from the subject, according to the sampling method employed.

In addition, comparable bioavailability was achieved with the coated tablets of the present invention, both to values obtained in the previous study with the reference product and to values which were described in the literature (see for example the previously referenced article in *Pharmacokinetics*). Furthermore, the values obtained for Cmax and Tmax concerning the rate of absorption were comparable to results obtained in the previous study performed with the reference product, and as described in the literature (see for example the previously referenced article in *Pharmacokinetics*). Thus, the coated tablets of the present invention clearly show good performance both *in vitro*, as described in Example 6, and *in vivo*.

Example 8

Coated pellets were prepared according to the process previously described above in Example 4. However, the pellets were coated with the following suspension:

Enteric coating (quantities per capsule)

HPMCAS	21.00 mg
Triethyl Citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
Colloidal silicon dioxide	2.10 mg
Sodium hydroxide	1.12 mg

Example 9

Although the previous Examples used aqueous solutions for providing an optimal coating, the possibility of increasing the concentration of the enteric coating polymer by using an alcohol-based solution was studied in this Example.

Coated pellets were prepared according to the process of Example 4, except that these pellets were coated with the following solution, to obtain the required protection in an acidic environment.

Enteric coating

	Solution prepared	**Quantities per capsule**
Alcohol 95%	1.900 kg	N/A
Water	0.830 kg	N/A
HPMCAS	0.476 kg	21.00 mg
Triethyl citrate	0.136 kg	6.00 mg
Sodium lauryl sulfate	0.015 kg	0.66 mg
Colloidal silicon dioxide	0.047 kg	2.1 mg
Sodium hydroxide	0.025 kg	1.12 mg

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Example 10

Substrate (Active Compressed Tablet Core)

Ingredients	Quantity per tablet
Omeprazole	20mg
Lactose	203mg
Magnesium carbonate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

Enteric coating layer

Ingredients	Quantity per tablet
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™ (pink pigment)	10.8mg

For the preparation of the substrate, Omeprazole was mixed together thoroughly with lactose, sodium starch glycolate, magnesium carbonate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. These tablets were then

transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4, with the addition of a pigment to the enteric coating material.

Example 11

Stability tests were performed with the formulation prepared according to Example 10. For the tests, the tablets were packed into alu-alu blister. The blister was then stored under room temperature or under accelerated conditions of 30°C and 60% relative humidity (RH), or 40°C and 75% relative humidity. Samples of the tablets were examined initially and after 6 months of storage under one of these conditions. In addition samples were assayed. A dissolution test was performed, and gastric resistance was also examined. The tablet gave good stability results even after storage at 40°C. The results are shown in the table below.

Test performed	Initial	25°C 6 month	30°C / 60%RH 6 month	40°C / 75%RH 6 month
Visual Description	conform	conform	conform	conform
Assay	19.76mg per tablet	20.19mg per tablet	19.97mg per tablet	19.28mg per tablet
Dissolution	96%	96%	96%	96%
Gastric Resistance	96%	96%	95%	94%

Example 12

A two-way pharmacokinetic study was performed in vivo for testing the bioequivalence of the coated tablets which were prepared according to Example 10, as compared to the reference product which is the 20mg Omeprazole dosage form of the formulation of Astra (Sweden), called Losec™. The study was performed on 39 volunteers. As shown in the table below, the results of the study showed that the two products exhibited very similar pharmacokinetic profiles, such that the two formulations

can be considered to be bioequivalent.

Formulation	AUC (ng x hour/ml)	Cmax (ng/ml)	Tmax (hours)
Formulation of the present invention (Example 10)	426 ± 256	217 ± 109	1.08 ± 0.64
Losec™ (Astra)	434 ± 226	246 ± 113	1.56 ± 0.79

Example 13

Substrate (Active Compressed Tablet Core)

Ingredients	Quantity per tablet
Omeprazole	20mg
Lactose	203mg
Sodium hydrogen carbonate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

Enteric coating layer

Ingredients	Quantity per tablet
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™	10.8mg

For the preparation of the substrate, Omeprazole was thoroughly mixed together with lactose, sodium starch glycolate, sodium hydrogen carbonate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. .These tablets were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 14

Substrate (Active Compressed Tablet Core)

Ingredients	Quantity per tablet
Omeprazole	20mg
Lactose	203mg
Trisodium citrate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

Enteric coating layer

Ingredients	Quantity per tablet
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™	10.8mg

For the preparation of the substrate, Omeprazole was mixed thoroughly together with lactose, sodium starch glycolate, trisodium citrate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. These tablets were then

transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 15

Stability tests were performed with the formulations prepared according to Examples 10, 13 and 14. Both coated and non-coated tablets were placed into an open box and stored at 40°C and 75% relative humidity, which are very stringent conditions. The coated and uncoated tablets were examined initially after 1 week and again after 2 weeks to determine stability. The results are shown in the tables below.

Tablets prepared according to Example 10

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

Tablets prepared according to Example 13

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

Tablets prepared according to Example 14

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

Example 16

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution. Hard gelatin capsules were then filled with the resultant pellets.

Substrate

Neutral core	Quantity per capsule
Sugar spheres 20/25 (700-850 microns)	110 mg

Active coating

Ingredients	Quantity per capsule
Omeprazole	20.00 mg
Hydroxypropyl methylcellulose 2910	5.00 mg
Hydroxypropyl cellulose	6.00 mg
Sodium stearate	0.13 mg
Sodium lauryl sulfate	0.50 mg

Enteric coating layer

HPMCAS	21.00 mg
Triethyl citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
colloidal silicon dioxide	2.1 mg
Arginine	3.15 mg

The composition of the present invention was prepared according to this Example as follows. First, sugar spheres were placed in a fluid bed coating chamber, equipped with a Wurster bottom spraying device. A suspension of the ingredients in water was then prepared so that the concentration was approximately 20% of the total solids in water. This active coating suspension was sprayed onto the neutral sugar spheres.

A suspension of the enteric coating was prepared as follows. First, triethyl citrate was dissolved in water to form an aqueous solution. Sodium lauryl sulfate was then added to this aqueous solution. HPMCAS and colloidal silicon dioxide were dispersed in

this solution, such that the concentration of HPMCAS was about 10% weight per volume. Arginine (3% weight per volume solution) was added to adjust the pH value of the solution to a pH value in a range of from about pH 7 to about pH 9. The enteric coating was layered over the substrate in order to form the finished pellets. The pellets were then placed in capsules.

Example 17

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution. Hard gelatin capsules were then filled with the resultant pellets.

Substrate

Neutral core	**Quantity per capsule**
Sugar spheres 20/25 (700-850 microns)	110 mg

Active coating

Ingredients	Quantity per capsule
Omeprazole	20.00 mg
Hydroxypropyl methylcellulose 2910	5.00 mg
Hydroxypropyl cellulose	6.00 mg
Arginine	0.13 mg
Sodium lauryl sulfate	0.50 mg

Enteric coating layer

HPMCAS	21.00 mg
Triethyl citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
colloidal silicon dioxide	2.1 mg
Sodium hydroxide	1.12 mg

The composition of the present invention was prepared according to this Example as follows. First, sugar spheres were placed in a fluid bed coating chamber, equipped with a Wurster bottom spraying device. A suspension of the ingredients in water was then prepared so that the concentration was approximately 20% of the total solids in water. This active coating suspension was sprayed onto the sugar spheres.

A suspension of the enteric coating was prepared according to Example 8. The enteric coating was layered over the substrate in order to form to form the finished pellets. The pellets were then placed in capsules.

Example 18

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution. Hard gelatin capsules were then filled with the resultant pellets.

Substrate

Neutral core	**Quantity per capsule**
Sugar spheres 20/25 (700-850 microns)	110 mg

Active coating

Ingredients	**Quantity per capsule**
Omeprazole	20.00 mg
Hydroxypropyl methylcellulose 2910	5.00 mg
Hydroxypropyl cellulose	6.00 mg
Arginine	0.13 mg
Sodium lauryl sulfate	0.50 mg

Enteric coating layer

HPMCAS	21.00 mg
Triethyl citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
colloidal silicon dioxide	2.1 mg
Arginine	3.15 mg

The composition of the present invention was prepared according to this Example as follows. First, sugar spheres were placed in a fluid bed coating chamber, equipped with a Wurster bottom spraying device. A suspension of the ingredients in water was then prepared so that the concentration was approximately 20% of the total solids in water. This active coating suspension was sprayed onto the sugar spheres to form the substrate.

A suspension of the enteric coating was prepared according to Example 16. The enteric coating was layered over the substrate in order to form to form the finished pellets. The pellets were then placed in capsules.

Example 19

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution to form pellets. Hard gelatin capsules were then filled with the resultant pellets.

Substrate

Neutral core

Ingredients	Quantity per capsule
Sugar spheres 20/25 (700-800 microns)	110mg

Active coating

Ingredients	Quantity per capsule
Omeprazole	20 mg
Hydroxypropyl methylcellulose 2910	5 mg
Hydroxypropyl cellulose	6 mg
Sodium lauryl sulfate	0.5 mg
Arginine	0.1 mg

Enteric coating layer

Ingredients	Quantity per capsule
Triethyl citrate	35 mg
Sodium lauryl sulfate	3.8 mg
HPMCAS	126 mg
Colloidal silicon dioxide	19 mg
Talc	17 mg
Ammonia (in a 25% solution)	3 mg

The composition of the present invention was prepared according to this example as follows. First, sugar spheres were placed in a fluid bed-coating chamber, equipped with a Wurster bottom-spraying device. Next, a suspension of the ingredients in water was then prepared for a final concentration of the total solids of approximately 15% in water, to form the active coating. This active coating suspension was sprayed onto the sugar spheres, thereby forming the substrate.

A suspension of the enteric coating was then prepared as follows. First, triethyl citrate was dissolved in water to form an aqueous solution. Sodium lauryl sulfate was then added to this aqueous solution. HPMCAS, colloidal silicon dioxide and talc were dispersed in this solution, such that the concentration of HPMCAS was about 7% weight per volume. Ammonia in a 25% solution was added to adjust the pH value in a range of from about 7 to about pH 9. The enteric coating was layered over the substrate in order to form the finished pellets. The pellets were then placed in capsules.

Example 20

Substrate (active compressed tablet core)

Ingredients	**Quantity per capsule**
Omeprazole	20 mg
lactose	203 mg
Magnesium carbonate	10 mg
Sodium starch glycollate	10 mg
Sodium stearyl fumarate	7 mg

Enteric coating layer

Ingredients	**Quantity per capsule**
Triethyl citrate	4.5 mg
Sodium lauryl sulfate	0.5 mg
HPMCAS	16 mg
Talc	8.14 mg
Ammonia (in a 25% solution)	0.14 mg
Sepisperse ® (pink pigment)	10.8 mg
Isopropyl alcohol	N/A
Alcohol	N/A

The substrate of the prevent invention was prepared as described in Example 10. A suspension of the enteric coating was then prepared as follows. First, triethyl citrate was dissolved in a mixture of isopropyl alcohol and alcohol. Sodium lauryl sulfate was then

added to this solution. HPMCAS and talc were dispersed in this solution, such that the concentration of HPMCAS was about 6% weight per volume. Ammonia in a 25% solution was added to adjust the pH value in a range of from about pH 7 to about pH 9. The pigment was then added to the enteric coating dispersion. The tablet cores were then transferred into a conventional coating pan and coated with the enteric coating layer.

Example 21

Substrate (active compressed tablet core)

Ingredients	**Quantity per capsule**
Omeprazole	10 mg
lactose	101.5 mg
Sodium stearate	5 mg
Sodium starch glycollate	5 mg
Sodium stearyl fumarate	3.5 mg

Enteric coating layer

Ingredients	Quantity per capsule
Triethyl citrate	2.25 mg
Sodium lauryl sulfate	0.25 mg
HPMCAS	8 mg
Talc	4.7 mg
Sodium hydroxide	0.43 mg
Sepisperse ® (pink pigment)	5.4 mg

For the preparation of the substrate, Omeprazole was mixed together thoroughly with lactose, sodium starch glycollate, sodium stearate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 125 mg each. These tablet were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 10.

Example 22

Stability tests were performed with the formulation prepared according to Example 21. For the tests, the tablets were packed into alu-alu blister. The blister was then stored under room temperature or under accelerated conditions of 30°C and 60% relative humidity (RH), or 40°C and 75% relative humidity. Samples of these tablets were examined initially and after 6 months of storage under one of these conditions. In addition samples were assayed and purity test was performed. A dissolution test was

performed, and gastric resistance was also examined. The tablet gave good stability results even after storage at 40°C. The results are shown in the table below.

Test performed	Initial	25°C 6 months	30°C/60%RH 6 months	40°C/75%RH 6 months
Description	conform	conform	conform	conform
Assay	98.4%	96.7%	96.9%	96.3%
Dissolution	95%	97%	95%	95%
gastric resistance	96%	95%	97%	96%
individual impurity total impurity	0.04% 0.04%	not detectable not detectable	not detectable not detectable	0.23% 0.29%

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While the invention has been described with respect to a limited number of embodiments, it will be appreciated that many variations, modifications and other applications of the invention may be made.

WHAT IS CLAIMED IS:

1. A stable composition for a benzimidazole derivative, the composition comprising:

(a) a substrate, said substrate featuring the benzimidazole derivative; and

(b) an enteric coating material layered directly over said substrate, said enteric coating material having a pH value of at least about 6.5, thereby obviating the need for an intermediate layer between said substrate and said enteric coating, with the proviso that said enteric coating material does not include HPMCP (hydroxypropyl methylcellulose phthalate).

2. The composition of claim 1, wherein said substrate is an active core for containing the benzimidazole derivative.

3. The composition of claim 2, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet.

4. The composition of claim 2, wherein said active core is a tablet formed by compression.

5. The composition of claim 1, wherein said substrate features:

(i) a neutral core; and

(ii) an active coating containing the benzimidazole derivative, said active coating being layered over said neutral core;

such that the composition is in a form of a pellet.

6. The composition of claim 5, wherein said active coating includes at least one polymer.

7. The composition of claim 6, wherein said at least one polymer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC).

8. The composition of claim 6, wherein said active coating includes a combination of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC).

9. The composition of claim 6, wherein said active coating includes a basic stabilizing material.

10. The composition of claim 9, wherein said basic stabilizing material includes at least one of sodium stereate and arginine.

11. The composition of claim 1, wherein said substrate includes a basic stabilizing material.

12. The composition of claim 11, wherein said basic stabilizing material includes at least one of sodium stereate, arginine, magnesium carbonate and sodium hydrogen carbonate.

13. The composition of claim 1, wherein said substrate features a core containing the benzimidazole derivative with a suitable binding agent, said core being prepared by spheronisation and pelletization; such that the composition is in a form of a pellet.

14. The composition of claim 1, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

15. The composition of claim 14, wherein said enteric coating material further comprises an alkaline compound, such that said pH value is adjusted by adding said alkaline compound to said enteric material.

16. The composition of claim 15, wherein said alkaline compound is an inorganic alkaline compound.

17. The composition of claim 16, wherein said alkaline compound is selected from the group consisting of basic sodium, potassium and ammonium hydroxide.

18. The composition of claim 17, wherein said enteric coating material is at least about 60 % neutralized by adding said alkaline compound.

19. The composition of claim 18, wherein said enteric coating material is at least about 80 % neutralized by adding said alkaline compound.

20. The composition of claim 18, wherein said enteric coating material is at least about 95 % neutralized by adding said alkaline compound.

21. The composition of claim 15, wherein said pH value is in a range of from about 7 to about 10.

22. The composition of claim 15, wherein said enteric coating material further comprises a plasticizer.

23. The composition of claim 22, wherein said plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

24. The composition of claim 1, wherein the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof.

25. A stable composition for a benzimidazole derivative, the composition consisting essentially of:

(a) a substrate, said substrate featuring the benzimidazole derivative; and

(b) an enteric coating material layered over said substrate, said enteric coating material having a pH value of at least about 6.5 by an alkaline compound, such that said pH value is adjusted by adding said alkaline compound to said enteric material.

26. The composition of claim 25, wherein said substrate is an active core for containing the benzimidazole derivative.

27. The composition of claim 26, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet, said active core being formed by embedding the benzimidazole derivative in poloxamer.

28. The composition of claim 26, wherein said active core is a tablet formed by compression.

29. The composition of claim 25, wherein said substrate features:

(i) a neutral core; and

(ii) an active coating containing the benzimidazole derivative, said active coating being layered over said neutral core.

30. The composition of claim 29, wherein said active coating includes at least one polymer.

31. The composition of claim 30, wherein said at least one polymer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC).

32. The composition of claim 30, wherein said active coating includes a combination of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose. (HPC).

33. The composition of claim 29, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

34. The composition of claim 33, wherein said alkaline compound is an inorganic alkaline salt compound.

35. The composition of claim 34, wherein said alkaline compound is selected from the group consisting of basic sodium, potassium or ammonium hydroxide.

36. The composition of claim 35, wherein said enteric coating material is at least about 60 % neutralized by adding said alkaline compound.

37. The composition of claim 36, wherein said enteric coating material is at least about 80 % neutralized by adding said alkaline compound.

38. The composition of claim 37, wherein said enteric coating material is at least about 95 % neutralized by adding said alkaline compound.

39. The composition of claim 34, wherein said pH value is in a range of from about 7 to about 10.

40. The composition of claim 34, wherein said enteric coating material further comprises a plasticizer.

41. The composition of claim 40, wherein said plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

42. The composition of claim 25, wherein the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof.

43. A method for producing a stable composition for a benzimidazole derivative, the method comprising:

forming a substrate with the benzimidazole derivative;

preparing an enteric coating material having a pH value of at least about 6.5; and

layering said enteric coating material directly over said substrate, with the proviso that said enteric coating material does not include HPMCP (hydroxypropyl methylcellulose phthalate).

44. The method of claim 43, wherein said substrate is formed by melting poloxamer and by mixing the benzimidazole derivative into said poloxamer.

45. The method of claim 43, wherein said substrate is formed by direct compression.

46. The method of claim 43, wherein said substrate is formed by wet granulation.

47. The method of claim 43, wherein said substrate is formed by coating on an inert core.

48. The method of claim 43, wherein said enteric coating material is prepared by:

mixing an enteric material with water to form a mixture; and

adding an alkaline compound to said mixture to form an aqueous solution having a pH value of from about 7 to about 10.

49. The method of claim 43, wherein said enteric coating material is prepared by:

mixing an enteric material with water and alcohol to form a mixture; and

adding an alkaline compound to said mixture to form an aqueous solution having a pH value of from about 7 to about 10.

ABSTRACT OF THE DISCLOSURE

A stable composition with a benzimidazole derivative, such as Omeprazole, which does not contain a separating layer between the active compound and an enteric coating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the optional addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this pH range, the enteric coating is optionally applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material. The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach. The problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the enteric coat at this stage is no longer acidic.